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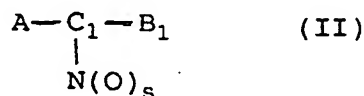
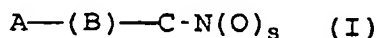
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*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

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(54) Title: PHARMACEUTICAL COMPOUNDS



(57) Abstract: Compounds or their salts having general formulas (I) and (II): wherein s is and integer equal to 1 or 2, preferably s = 2; A is the radical of a drug and is such as to meet the pharmacological tests reported in the description, C and C<sub>1</sub> are two bivalent radicals. The precursors of the radicals B and B<sub>1</sub> are such as to meet the pharmacological test reported in the description.



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# INTERNATIONAL SEARCH REPORT

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## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C203/04 C07C327/34 C07D209/28 C07D233/64 C07D495/04  
 C07C211/49 C07F9/38 C07D295/088 C07D207/16 C07D499/32  
 C07D473/08 C07C211/42 C07D219/10 C07D307/30 C07D401/14

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D C07F C07H A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

BEILSTEIN Data, WPI Data, EPO-Internal, PAJ, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 052 910 A (REINER ALBERTO & C) 2 June 1982 (1982-06-02) the whole document ---	1,8-10
A	EP 0 255 164 A (ZAMBON) 3 February 1988 (1988-02-03) the whole document ---	1,8-10
A	CHEMICAL ABSTRACTS, vol. 107, no. 7, 17 August 1987 (1987-08-17) Columbus, Ohio, US; abstract no. 59488w, page 781; XP002164473 abstract -& ES 8 609 231 A (FARMHISPANIA) 10 December 1986 (1986-12-10) --- -/--	1,8-10



Further documents are listed in the continuation of box C.



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Date of the actual completion of the international search

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Date of mailing of the international search report

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## A. CLASSIFICATION OF SUBJECT MATTER

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Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

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Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 103 320 A (EDMOND PHARMA) 21 March 1984 (1984-03-21) example 3 ---	1,8-10
A	WO 98 47534 A (KLINGE PHARMA) 29 October 1998 (1998-10-29) page 12 -page 13 ---	1,8-10
A	US 5 597 847 A (J.A. MATJI, ET AL.) 28 January 1997 (1997-01-28) column 1, line 47 - line 67; examples 1,2 --- -/--	1,8-10

☒ Further documents are listed in the continuation of box C.

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>G. CIRINO, ET AL.: "Inhibition of inducible nitric oxide synthase expression by novel nonsteroidal anti-inflammatory derivatives with gastrointestinal sparing properties"</p> <p>BRITISH JOURNAL OF PHARMACOLOGY, vol. 117, no. 7, April 1996 (1996-04), pages 1421-1426, XP000938504</p> <p>Stockton Press, Basingstoke, GB</p> <p>ISSN: 0007-1188</p> <p>the whole document</p>	1,8-10
A	<p>G. BENINI, ET AL.: "Plasma concentrations and pharmacokinetic parameters of nitrofenac using a simple and sensitive HPLC method"</p> <p>JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 84, no. 1, January 1995 (1995-01), pages 93-95, XP002164443</p> <p>American Pharmaceutical Association, Washington, DC, US</p> <p>ISSN: 0022-3549</p> <p>the whole document</p>	1,8-10
A	<p>US 5 861 426 A (P. DEL SOLDATO, ET AL.)</p> <p>19 January 1999 (1999-01-19)</p> <p>column 2, line 51 - line 67; examples</p>	1,8-10

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,2 4-10 (not searched in part), 3 (not searched)

Present claims 1-10 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Furthermore, present claims 1-10 relate to compounds defined by reference to a desirable characteristic or property, namely that their precursors attain a certain level of anti-oxidative activity evidenced according to test 4 (which is elucidated in claim 1) and at least a certain level of at least one of (a) gastrointestinal damage, (b) apoptosis or (c) hepatic damage and/or gastric damage and/or cardiovascular damage evidenced according to tests 1 to 3 (also elucidated in claim 1). Since the combination of these properties (anti-oxidative activity and lower toxicity) is in fact the problem to be solved by the compounds of the present application (see page 9, lines 1-11 of the description), this means that the claimed compounds are defined in terms of their being a solution to this problem.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds prepared in examples 1-28.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/03234

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0052910	A	02-06-1982	IT 1134458 B	13-08-1986
			CH 648297 A	15-03-1985
			DE 3169890 D	15-05-1985
			JP 1028744 B	05-06-1989
			JP 1543778 C	15-02-1990
			JP 57167963 A	16-10-1982
EP 0255164	A	03-02-1988	IT 1213301 B	20-12-1989
			AT 96150 T	15-11-1993
			AT 179071 T	15-05-1999
			DE 3752272 D	27-05-1999
			DE 3752272 T	30-12-1999
			DE 3787844 D	25-11-1993
			DE 3787844 T	10-02-1994
			EP 0565146 A	13-10-1993
			ES 2060592 T	01-12-1994
			ES 2133351 T	16-09-1999
			GR 3030822 T	30-11-1999
			JP 63023857 A	01-02-1988
			US 4806567 A	21-02-1989
			US 4812477 A	14-03-1989
ES 8609231	A	16-12-1986	ES 549540 D	01-09-1986
EP 0103320	A	21-03-1984	IT 1190987 B	24-02-1988
			AT 27270 T	15-06-1987
			BE 897617 A	16-12-1983
			CA 1202317 A	25-03-1986
			DE 3371627 D	25-06-1987
			FR 2532647 A	09-03-1984
			US 4563443 A	07-01-1986
WO 9847534	A	29-10-1998	AU 2387997 A	13-11-1998
			EP 0971743 A	19-01-2000
US 5597847	A	28-01-1997	IT 1256345 B	01-12-1995
			DE 69305322 D	14-11-1996
			DE 69305322 T	20-02-1997
			EP 0609415 A	10-08-1994
			GR 3021404 T	31-01-1997
			HK 1006967 A	26-03-1999
			JP 7500355 T	12-01-1995
			RU 2109009 C	20-04-1998
			AT 143941 T	15-10-1996
			CA 2120942 A	03-03-1994
			DK 609415 T	18-11-1996
			WO 9404484 A	03-03-1994
			ES 2093979 T	01-01-1997
US 5861426	A	19-01-1999	IT 1269735 B	15-04-1997
			IT 1274609 B	18-07-1997
			AU 702662 B	25-02-1999
			AU 2215695 A	29-11-1995
			BR 9507634 A	23-09-1997
			DE 69512232 D	21-10-1999
			DE 69512232 T	24-02-2000
			DK 759899 T	20-12-1999
			EP 0759899 A	05-03-1997

## INTERNATIONAL SEARCH REPORT

### Information on patent family members

Internal Application No.

PCT/EP 00/03234

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5861426 A		GR 3032078 T	31-03-2000
		JP 9512798 T	22-12-1997
		SI 759899 T	31-12-1999
		AT 168986 T	15-08-1998
		AT 184589 T	15-10-1999
		AU 678063 B	15-05-1997
		AU 7809294 A	01-05-1995
		BR 9407749 A	12-02-1997
		CA 2173582 A	13-04-1995
		CA 2190087 A	16-11-1995
		DE 69412109 D	03-09-1998
		DE 69412109 T	21-01-1999
		DK 722434 T	16-11-1998
		WO 9509831 A	13-04-1995
		WO 9530641 A	16-11-1995
		EP 0722434 A	24-07-1996
		ES 2120070 T	16-10-1998
		ES 2139199 T	01-02-2000
		HU 74446 A, B	30-12-1996
		HU 75961 A	28-05-1997
		JP 9503214 T	31-03-1997
		RU 2136653 C	10-09-1999
		SI 722434 T	31-12-1998
		US 5700947 A	23-12-1997
		US 5780495 A	14-07-1998